

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 October 2002 (17.10.2002)

PCT

(10) International Publication Number
WO 02/081449 A1

(51) International Patent Classification:
C07D 211/58,
401/14, 211/96, 417/14, A61K 3/14468

(CH) THOMA, Gerhard [DE/DE]; Tailing 32, D-79540
Lörnach (DE); ZERWES, Hans-Günter [DE/DE]; Holz-
gasse 55, D-79539 Lörnach (DE).

(21) International Application Number: PCT/EP0203871

(22) International Filing Date: 8 April 2002 (08.04.2002)

(74) Agent: BECKER, Konrad; Novartis AG, Corporate In-
tellectual Property, Patent & Trademark Dept., CH-4002
Basel (CH).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Date: 9 April 2001 (09.04.2001) GB
0108876.4

(71) Applicant (for all designated States except AT, US): NO-
VARTIS AG [CH/CH]; Lehnstrasse 35, CH-4002 Basel
(CH).

(71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN
VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT];
Brunner-Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and
(73) Inventor/Applicants (for US only): ALBERT, Rainer
[AT/CH]; Warenbergstrasse 21, CH-4052 Basel (CH);
BRUNS, Christian [DE/DE]; Ziegehofstrasse 120, 79110
Freiburg (DE); NUNINGER, François [FR/FR]; 11,
rue de l'Université, F-68370 Willenschau (FR); STREIF,
Markus [CH/CH]; Fiedenstrasse 15, CH-4127 Birsleiden

For two-letter code and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

Published:
with international search report

— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(84) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, FR, GB, GR, GU, HK,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LT, LU, LV, MA, MD, MG, MK, MN, MX, MY, NZ, OM, PA,
PE, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA,
US, UZ, VN, YU, ZA, ZW.

WO 02/081449

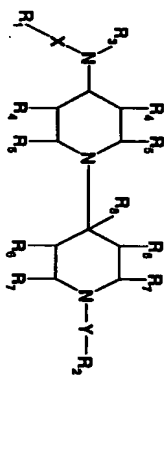
PCT/EP0203871

- 1 -

BIPERIDINYL-DERIVATIVES AND THEIR USE AS CHENOKINE RECEPTORS INHIBITORS

The present invention relates to piperidine derivatives, process for their production, their
uses and pharmaceutical compositions containing them.

More particularly, the present invention provides a compound of formula I



wherein

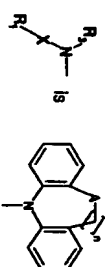
X is a direct bond; -CH2-; -CH2-CH2-; -CH(R8)-; -C(O)-; -O-; -NH- or NR8;

R1 is optionally R10 and/or R11-substituted phenyl; optionally R10 and/or R11-substituted
heteroaryl; optionally R10 and/or R11-substituted heteroaryl N-oxide; or optionally R10 and/or
R11-substituted naphthyl;

R2 has one of the significances given for R1; or is optionally R10 and/or R11-substituted
fluorenyl; optionally R10-substituted C1-C6 alkyl; optionally R10-substituted C2-C6 alkenyl;
optionally R10-substituted C3-C6 cycloalkyl; optionally R10-substituted adamantyl; or
optionally R10-substituted C4-C6 cycloalkenyl;

R3 has one of the significances given for R1; or is optionally R10 and/or R11-substituted
fluorenyl; R10-substituted C1-C6 alkyl; optionally R10-substituted C2-C6 alkenyl; optionally R10-
substituted C3-C6 cycloalkyl; optionally R10-substituted adamantyl; or optionally R10-
substituted C4-C6 cycloalkenyl;

or



wherein A is -CH2-, -NH-, -S-, -SO2- or -O-, n is 0, 1 or 2, and the aromatic rings
are each, independently optionally R10-substituted;

each of R4, independently, has one of the significances of R5; or is CN; OH; OR6; F; Cl; Br,
or I;

WO 02/081449 A1

(57) Abstract: Piperidine derivatives of formula (I) as disclosed in the specification have interesting pharmacological properties e.g.
as CCR5 inhibitors.

- 2 -

each of R_6 , independently, is H; C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; phenyl; benzyl; or heteroaryl;

each of R_6 , independently, has one of the significances given for R_4 ;

each of R_7 , independently, has one of the significances given for R_6 ;

R_4 is H; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; CN; CH_2NH_2 ; CH_2NHR_6 ; $CH_2NR_6R_6$; $CH_2NHC(O)R_6$; $CH_2NR_6C(O)R_6$; $CH_2NHC(O)NHR_6$; $CH_2NR_6C(O)NHR_6$; $CH_2NR_6C(O)NR_6R_6$; $CH_2NHC(O)OR_6$; $CH_2NR_6C(O)OR_6$; $CH_2NHSO_2R_6$; $CH_2N(SO_2R_6)_2$; or $CH_2NR_6SO_2R_6$;

each R_8 , independently, is C_1-C_6 alkyl; C_2-C_6 cycloalkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; heteroaryl; or CF_3 ;

R_{10} represents 1 to 4 substituents independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_2-C_6 cycloalkyl; C_2-C_6 alkenyl; C_2-C_6 cycloalkenyl; C_2-C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR₆; CONH₂; CONHR₆; CONR₆R₆; OC(O)R₆; OC(O)OR₆; OC(O)NHR₆; OC(O)NR₆R₆; OSO₂R₆; COOH; COOR₆; CF₃; CHF₂; CH₂F; CN; NO₂; NH₂; NHR₆; NR₆R₆; NHC(O)R₆; NR₆C(O)R₆; NHC(O)NHR₆; NHC(O)NH₂; NR₆C(O)NHR₆; NR₆C(O)NR₆R₆; NHC(O)OR₆; NR₆C(O)OR₆; NHSO₂R₆; N(SO₂R₆)₂; NR₆SO₂R₆; SR₆; Si(O)R₆; SO₂R₆; Si(CH₃)₃ and BOC(CH₂)₂;

R_{11} represents two adjacent substituents which form an annulated 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; and

Y is a direct bond; -C(O)-; -C(O)CH₂-; -S(O)-; -S(O)₂-; -C(S)-; -CH₂-; -C(CH₂-CH₂-); -CH(R₆)- or -C(R₆)₂-;

in free form or in salt form.

Any alkyl, alkenyl or alkynyl may be linear or branched. Halogeno is F, Cl, Br or I.

By heteroaryl is meant an aromatic ring system comprising mono-, bi- or tricyclic systems which contains up to 4 heteroatoms independently selected from N, O and S, such as for example furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazinyl, tetrazinyl, indolyl, benzothienophenyl, benzofuranyl, benzimidazolyl, indazolyl, benzothiazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl or naphthyridinyl.

Preferred annulated 4-7 membered non-aromatic ring as represented by R_{11} , is annulated 5 or 6 membered non aromatic ring optionally containing 1 or 2 oxygen and include e.g.

- 3 -

-O-CH₂-O- or -O-CH₂-CH₂-O-, attached to 2 adjacent carbon atoms.

The compounds of formula I may exist in free form or in salt form, e.g. addition salts with e.g. organic or inorganic acids, for example, hydrochloric acid, acetic acid when R_{11} , R_6 , and/or R_3 comprises an optionally substituted amino group or a heterocyclic residue which can form addition salts. When the compounds of formula I have one or more asymmetric centers in the molecule, e.g. when a piperidine ring is substituted, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof.

In the compounds of formula I, the following significances are preferred individually or in any sub-combination:

1. R_1 is optionally R_{10} -substituted phenyl; optionally R_{10} -substituted heteroaryl; or optionally R_{11} -substituted phenyl.
2. R_2 is optionally R_{10} -substituted phenyl; optionally R_{10} -substituted heteroaryl; optionally R_{10} -substituted heteroaryl N-oxide; or optionally R_{10} -substituted naphthyl.
3. R_3 is optionally R_{10} -substituted phenyl; optionally R_{10} -substituted heteroaryl; or optionally R_{10} -substituted naphthyl.
4. Each of R_4 , R_5 , R_6 or R_7 , independently, is H; C_1-C_6 alkyl; or benzyl.
5. R_8 is H; C_1-C_6 alkyl; or C_2-C_6 alkenyl.
6. R_9 is C_1-C_6 alkyl; C_2-C_6 cycloalkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; heteroaryl; or CF_3 .
7. R_{10} represents 1 to 3 substituents independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_2-C_6 cycloalkyl; C_2-C_6 alkenyl; C_2-C_6 cycloalkenyl; C_2-C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR₆; CONH₂; CONHR₆; CONR₆R₆; OC(O)R₆; OC(O)OR₆; OC(O)NHR₆; OC(O)NR₆R₆; OSO₂R₆; COOH; COOR₆; CF₃; CHF₂; CH₂F; CN; NO₂; NH₂; NHR₆; NR₆R₆; NHC(O)R₆; NR₆C(O)R₆; NHC(O)NHR₆; NHC(O)NH₂; NR₆C(O)NHR₆; NR₆C(O)NR₆R₆; NHC(O)OR₆; NR₆C(O)OR₆; NHSO₂R₆; N(SO₂R₆)₂; NR₆SO₂R₆; SR₆; Si(O)R₆; SO₂R₆ and Si(CH₃)₃.
8. R_{11} represents -O-CH₂-O- attached on 2 adjacent carbon atoms.
9. X is a direct bond or -CH₂-.
10. Y is -C(O)-.

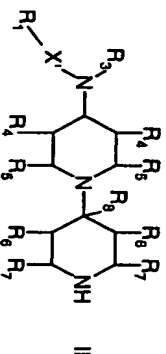
- 4 -

In the preferred compounds of formula I, R_0 may represent 1-3 substituents selected from C_1 -alkyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR₆; CONH₂; CONHR₆; CONR₆R₆; COOH; COOR₆; CF₃; CHF₂; CH₂F; NH₂; NHR₆; NR₆R₆; NHC(O)R₆; NR₆C(O)R₆; NHC(O)NHR₆; NHC(O)NH₂; NR₆C(O)NHR₆; NR₆C(O)NR₆R₆; NHC(O)OR₆ and NR₆C(O)OR₆.

R_0 is preferably C_1 - C_6 alkyl; C_3 - C_6 cycloalkyl; phenyl; benzyl; or heteroaryl; more preferably C_1 - C_6 alkyl.

The present invention also includes a process for the preparation of a compound of formula I which process comprises

- a) for the preparation of a compound of formula I wherein X is a direct bond, $-CH_2-$, $-CH_2-CH_2-$ or $-CHR_p-$ and Y is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O)_2-$, amidating a compound of formula II



wherein R_1 and R_2 are as indicated above and X' is a direct bond, $-CH_2-$, $-CH_2-CH_2-$ or $-CHR_p-$

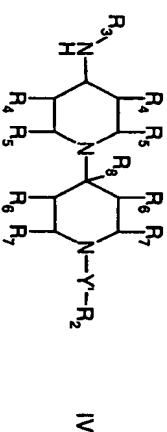
with a compound of formula III



wherein R_2 is as defined above, Y' is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O)_2-$ and A' is a leaving group, e.g. Cl or Br,

- b) for the preparation of a compound of formula I wherein X is a direct bond and Y is $-CH_2-$, substituting a compound of formula II as defined above wherein X' is a direct bond, to a reductive amination; or
- c) for the preparation of a compound of formula I wherein X is CH_2- , $-CH_2-CH_2-$ or $-CHR_p-$ and Y is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O)_2-$, reacting a compound of formula IV

- 5 -



wherein R_2 to R_6 and Y are as defined above, with a compound of formula V

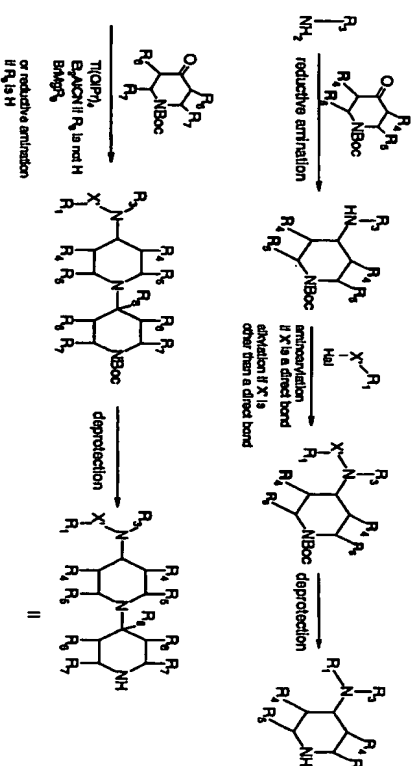


wherein R_1 is as defined above and X' is CH_2- or $-CHR_p-$;

and, where required, converting the resulting compound of formula I obtained in free form into the desired salt form, or vice versa.

The reaction steps a), b) or c) may be performed in accordance with methods known in the art or as disclosed in the Examples below. When R_0 comprises a group which should not participate in the reaction, this group may be protected in accordance with methods known in the art.

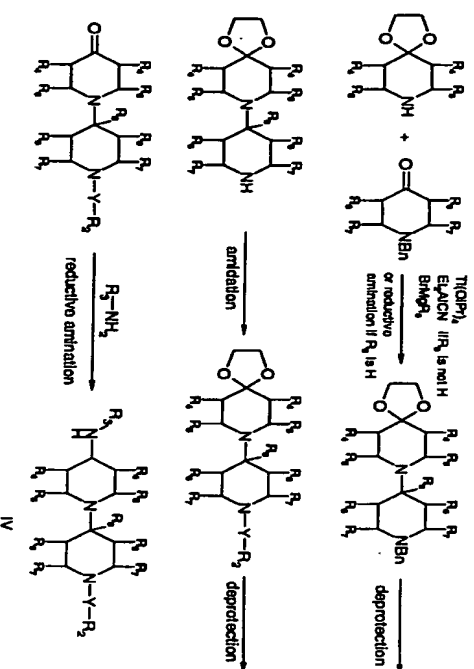
Compounds of formula II, used as starting material may be prepared as follows:



wherein X' and R_1 to R_8 are as defined above and Hal is Cl, Br or I. In above formulae, Boc is a protecting group which means tert-butyloxycarbonyl. This protecting group may be replaced in above reaction scheme by any amino protecting group, e.g. as disclosed in "Protective Groups in Organic Synthesis" by T. W. Greene, J. Wiley & Sons NY, 2nd ed., Chapter 7, 1991 and references therein, e.g. benzylloxycarbonyl or 9-fluorenylmethoxycarbonyl.

- 6 -

Compounds of formula IV, used as starting material, may be prepared as follows:



wherein R_2 to R_6 and Y are as defined above and Bn is benzyl.

Above reactions may be carried out in accordance with methods known in the art or as disclosed hereafter.

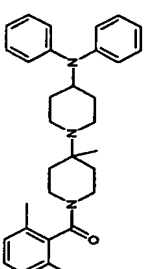
Insofar as the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as described hereafter.

The following Examples are illustrative of the invention, without limitation. Following abbreviations are used:

Bn	= Benzyl
Boc	= tert.-Butoxycarbonyl
DMF	= Dimethylformamide
DMSO	= Dimethylsulfoxide
BINAP	= 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
THF	= Tetrahydrofuran
TFA	= Trifluoroacetic acid
RT	= Room temperature

- 7 -

Example 1: (2,6-Dimethyl-phenyl)-(4-diphenylamino-4'-methyl-[1,4']bipiperdiny-1'-yl)-methanone



A mixture of (4'-Methyl-[1,4']bipiperdiny-4-yl)-diphenyl-amine (0.25 g, 0.71 mmol), 2,6-dimethylbenzoic acid (0.32 g, 2.13 mmol), 2-(1H-benzotriazole-1-yl)-1,3,3-tetramethyluronium tetrafluoroborate (0.57 g, 1.5 mmol), EtN(P)₂ (0.6 ml) and DMF (5 ml) is stirred for 16 h at 20°C. The mixture is diluted with t-butyl methyl ether (25 ml), washed with 2N NaOH (25 ml) and brine (25 ml) and dried with sodium sulfate. The solvent is removed and the residue purified by chromatography (SiO₂, t-butyl methyl ether/cyclohexane 1:4→1:0). The title compound is isolated as a colorless solid. MS/ESI 482 (M+H)⁺.

¹H NMR (400 MHz, DMSO) δ: 0.89 (3 H, s), 1.14-1.25 (3 H, m), 1.39 (1 H, m), 1.59 (1 H, m), 1.75 (1 H, m), 1.83-1.95 (2 H, m), 2.01 (3 H, s), 2.13 (3 H, s), 2.11-2.24 (2 H, m), 2.85 (2 H, m), 2.95 (1 H, m), 3.01 (1 H, m), 3.35 (1 H, m), 3.70-3.83 (2 H, m), 6.77 (4 H, m), 6.92-7.05 (4 H, m), 7.12 (1 H, m), 7.28 (4 H, m).

(4'-Methyl-[1,4']bipiperdiny-4-yl)-diphenyl-amine, used as starting material may be prepared as follows:

a) A mixture of phenyl-piperidin-4-yl-amine (4.14 g, 15.0 mmol), iodobenzene (3.06 g, 15.0 mmol), Pd(OAc)₂ (0.14 g, 0.63 mmol), BINAP (0.43 g, 0.69 mmol), t-BuOK (17.5 ml of 1M solution in THF) in toluene (20 ml) is heated at 110°C for 5 h. The mixture is diluted with ethyl acetate, extracted with sodium hydrogencarbonate and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO₂, t-butyl methyl ether/cyclohexane 1:9→1:1). 4-Diphenylamino-piperidine-1-carboxylic acid tert-butyl ester is isolated as a yellow solid. MS/ESI 353 (M+H)⁺.

b) A mixture of TFA (5 ml), methylene chloride (5 ml) water (0.25 ml) and 4-diphenylamino-piperidine-1-carboxylic acid tert-butyl ester (1.5 g, 4.2 mmol) is stirred for 2 h at 20°C.

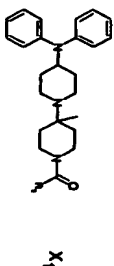
Sodium hydroxide (4N) is added and the mixture extracted with ethyl acetate. The organic

phase is dried with sodium sulfate and the solvent removed. Diphenyl-piperidin-4-yl-amine is isolated as a colorless oil. MS/ESI 253 (M+H)⁺

c) A suspension of diphenyl-piperidin-4-yl-amine (1.26 g, 5.00 mmol), 1-(tert-butyl oxy-carbonyl)-4-piperitone (1.00 g, 5.00 mmol), and titanium(IV) isopropoxide (1.42 g, 5.00 mmol) in 1,2-dichloroethane (25 ml) is stirred for 1 h at 80°C and then for 16 h at 20°C. Diethylaluminum cyanide (10 ml 1M solution in toluene) is added and the mixture stirred for additional 24 h. The solvent is removed and the crude material dissolved in tetrahydrofuran (25 ml). Methylmagnesium bromide (8.7 ml 3M solution in ether) is added dropwise and the mixture stirred for 3 h at 20°C. Ammonium chloride (10 % solution, 50 ml) and ethyl acetate (50 ml) are added, the organic phase washed with ammonium chloride (10 % solution, 50 ml) and sodium hydrogencarbonate (10 % solution, 50 ml), dried with sodium sulfate and the solvent removed. The residue is subjected to chromatography (SiO₂, ethyl acetate/cyclohexane 1:9→1:1). 4-Diphenylamino-4'-methyl-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester is isolated as a colorless solid MS/ESI 450 (M+H)⁺.

d) A mixture of trifluoroacetic acid (2 ml) and water (0.1 ml) is added dropwise to a solution of compound a) above (0.81 g, 1.80 mmol) in methylene chloride (5 ml) and the mixture stirred for 3 h at 20°C. Sodium hydrogencarbonate (10% solution, 10 ml) and ethyl acetate (20ml) are added and the organic phase dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (RP-18, methanol/H₂O 1:3→0:1). The title compound is isolated as a colorless oil. MS/ESI 350 (M+H)⁺; ¹H NMR (400 MHz, CDCl₃) δ = 0.88 (3 H, s), 1.35 (4 H, m), 1.60 (4 H, m), 1.83 (2 H, m), 2.15 (2 H, m), 2.58 (2 H, m), 2.87 (2 H, m), 2.98 (2 H, m), 3.78 (1 H, m), 6.78 (4 H, m), 6.94 (2 H, m), 7.22 (4 H, m).

By following the procedure of Example 1 and using as starting material (4'-methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine, the compounds of formula X₁











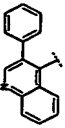




wherein R₂ has the significances as given in Table 1, may be prepared.






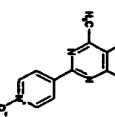






Table 1

Example	R ₂	MS/ESI (M+H) ⁺
2		483
3		499
4		460
5		454
6		470
7		522
8		468
9		484
10		560
11		514
12		561
13		488

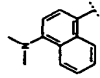

- 10 -

14		523
15		504
16		500
17		506
18		539
19		498
20		525
21		488
22		508
23		505
24		581
25		535
26		505

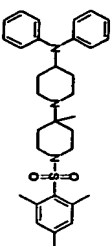
- 11 -

27		506
28		521
29		505
30		505
31		518
32		577
33		511
34		493
35		493
36		530
37		528
38		548

- 12 -

39		547
40		519

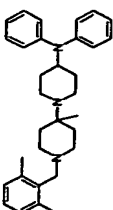
Example 41: [4'-Methyl-[1,4']bipiperidinyl-4-yl]-diphenyl-amine



A mixture of (4'-methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine (70 mg, 0.20 mmol) and 2,4,6-trimethyl-benzenesulfonyl chloride (65 mg, 0.30 mmol) and diisopropyl ethylamine (0.50 ml) in methylene chloride (3 ml) is stirred for 4h at RT. The mixture is diluted with ethyl acetate, extracted with sodium hydrogencarbonate (10 % solution) and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO₂, *t*-butyl methyl ether/cyclohexane 1:9→1:0). The title compound is isolated as a colorless solid.

MS/ESI 532 (M+H)⁺

Example 42: [1'-(2,6-Dimethyl-benzyl)-4'-methyl-[1,4']bipiperidinyl-4-yl]-diphenyl-amine



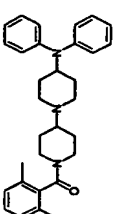
A mixture of (4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine (70 mg, 0.20 mmol) and 2,6-dimethyl-benzaldehyde (34 mg, 0.25 mmol) and Na(OAc)₂BH (63 mg, 0.25 mmol) in 1,2-dichloroethane (10 ml) is stirred at RT for 16 h. The mixture is diluted with ethyl acetate, extracted with sodium hydrogencarbonate (10 % solution) and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO₂, *tert*-butyl

- 13 -

methyl ether/methanol 1:0→10:1). The title compound is isolated as a colorless solid.

MS/ESI 468 (M+H)⁺

Example 43: (2,6-Dimethyl-phenyl)-(4-diphenylamino-[1,4']bipiperidinyl-1'-yl)-methanone



A mixture of TFA salt of [1,4']bipiperidinyl-4-yl)-diphenyl-amine (77 mg, 0.23 mmol), 2,6-dimethylbenzoic acid (100 mg, 0.67 mmol), 2-(1H-benzotriazole-1-yl)-1,3,3-tetramethyluronium tetrafluoroborate (254 mg, 0.67 mmol), EINI-Py₂ (2 ml) and DMF (3 ml) is stirred for 5 h at RT. The mixture is diluted with *tert*-butyl methyl ether (10 ml), washed

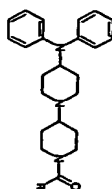
with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue purified by chromatography (SiO₂, *t*-butyl methyl ether/cyclohexane 1:1→ethyl acetate→ethyl acetate/H₂O 98:2). The title compound is isolated as a colorless solid.

MS/ESI 468 (M+H)⁺

[1,4'] Bipiperidinyl-4-yl)-diphenylamine, used as starting materials, may be prepared as follows:

- A mixture of diphenyl-piperidin-4-yl-amine (1.06 g, 4.2 mmol), 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (1.0 g, 5.0 mmol), AcOH (0.62 g, 10.3 mmol) and Na(OAc)₂BH (1.0 g, 4.7 mmol) in 1,2-dichloroethane (15 ml) is stirred for 4h at 65°C. The mixture is diluted with *t*-butyl methyl ether, extracted with 1N NaOH and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO₂, *t*-butyl methyl ether/cyclohexane 1:9→1:0). 4-Diphenylamino-[1,4']bipiperidinyl-1'-carboxylic acid *tert*-butyl ester is isolated as a colorless solid. MS/ESI 436 (M+H)⁺
- A mixture of 4-Diphenylamino-[1,4']bipiperidinyl-1'-carboxylic acid *tert*-butyl ester (1.06 g, 2.4 mmol), TFA (2.5 ml), H₂O (0.25 ml) and methylene chloride (5 ml) is stirred at RT for 4 h. The mixture is added dropwise to ether and the precipitate formed is filtered off. The TFA salt of [1,4']bipiperidinyl-4-yl)-diphenyl-amine is isolated as a colorless solid. MS/ESI 336 (M+H)⁺

By following the procedure of Example 2 above and using as starting materials [1,4]bipiperidin-4-yl-diphenyl-amine the compounds of formula X₂

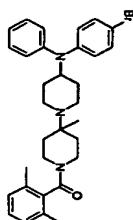


wherein R₂ has one of the significances given in Table 2, may be prepared

Table 2

Example	R ₂	MS/ESI
44		469
45		485
46		470
47		509
48		486
49		547
50		525

Example 51: (4-[(4-bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidin-1'-yl)-(2,6-dimethyl-phenyl)-methanone



A mixture of [4-(4-bromo-phenylamino)-4'-methyl-[1,4']bipiperidin-1'-yl]-(2,6-dimethyl-phenyl)-methanone (97 mg; 0.20 mmol), iodobenzene (41 mg; 0.20 mmol), Pd (OAc)₂ (1.9 mg; 0.008 mmol), BINAP (5.7 mg; 0.009 mmol) and *t*-BuOK (0.23 ml of 1 M solution on THF) in toluene (3 ml) is heated at 110°C for 16h. The mixture is diluted with ethyl acetate and filtered. The resulting solution is extracted with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (first SiO₂, *t*-butyl methyl ether/cyclohexane 1:4→1:0 and subsequently RP-18, methanol/H₂O 7:3). The title compound is isolated as a colorless solid. MS/ESI 560 (M+H)⁺.

[4-(4-bromo-phenylamino)-4'-methyl-[1,4']bipiperidin-1'-yl]-(2,6-dimethylphenyl)-methanone, used as starting material, may be prepared as follows:

a) 8-(1-Benzyl-4-methyl-piperidin-4-yl)-1,4-dioxo-8-aza-spiro[4.5]decane is prepared from 1,4-dioxo-8-aza-spiro[4.5]decane and 1-benzyl-piperidin-4-one following a procedure as described in example 1c). MS/ESI 331 (M+H)⁺.

b) A mixture of 8-(1-benzyl-4-methyl-piperidin-4-yl)-1,4-dioxo-8-aza-spiro[4.5]decane (2.0 g, 6.1 mmol) and Pd(OH)₂ (20%) on charcoal (1 g) in methanol (30 ml) is hydrogenated for 16h at RT. The catalyst is filtered off and the solvent removed. Crude 8-(4-methyl-piperidin-4-yl)-1,4-dioxo-8-aza-spiro[4.5]decane is isolated as a yellow oil. MS/ESI 241 (M+H)⁺.

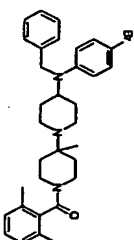
c) (2,6-Dimethyl-phenyl)-[4-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-4-methyl-piperidin-1'-yl]-methanone is obtained from crude 8-(4-methyl-piperidin-4-yl)-1,4-dioxo-8-aza-spiro[4.5]decane and 2,6-dimethyl-benzoyl acid by following a procedure as described in example 1. MS/ESI 373 (M+H)⁺.

d) A solution of (2,6-dimethyl-phenyl)-[4-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-4-methyl-piperidin-1'-yl]-methanone (915 mg, 2.46 mmol) in dioxan (30 ml) and HCl (6N; 30ml) is stirred for 4h at 50°C. The mixture is diluted with ethyl acetate (50 ml), extracted with 2N NaOH and brine and dried with sodium sulfate. Removal of the solvent affords 1'-(2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidin-4-one is isolated as a colorless solid. MS/ESI 328 (M+H)⁺.

- 16 -

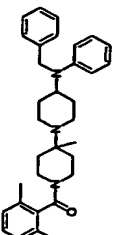
e) A mixture of 1'-(2,6-dimethyl-benzoyl)-4'-methyl-1,4'-bipiperidiny-4-one (49.3 mg; 0.15 mmol), 4-bromo-phenylamine (29 mg; 0.165 mmol), acetic acid (18 mg; 0.30 mmol) and $\text{NaBH}(\text{OAc})_3$ (35 mg; 0.165 mmol) in $(\text{CH}_2\text{Cl})_2$ (4 ml) is stirred for 16h at RT. The mixture is diluted with ethyl acetate, extracted with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (RP-18, methanol/ H_2O 8:2 \rightarrow 1:0). [4-(4-bromo-phenylamino)-4'-methyl-1,4'-bipiperidiny-1'-yl]-2,6-dimethyl-phenyl-methanone is isolated as a colorless solid. MS/ESI 484 ($\text{M}+\text{H}$) $^+$.

Example 52: [4-(Bromo-phenyl-amino)-4'-methyl-1,4'-bipiperidiny-1'-yl]-2,6-dimethyl-phenyl-methanone



A mixture of [4-(4-bromo-phenyl)-phenyl-amino]-4'-methyl-1,4'-bipiperidiny-1'-yl]-2,6-dimethyl-phenyl-methanone (97 mg; 0.20 mmol), bromomethyl-benzene (376 mg; 2.2 mmol) and K_2CO_3 (138 mg; 1.0 mmol) in DMF (3 ml) is stirred at 100°C for 16h. The mixture is diluted with ethyl acetate, extracted with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (first SiO_2 , t-butyl methyl ether and subsequently RP-18, methanol/ H_2O 8:2). The title compound is isolated as a colorless solid. MS/ESI 574 ($\text{M}+\text{H}$) $^+$.

Example 53: [4-(Benzyl-phenyl-amino)-4'-methyl-1,4'-bipiperidiny-1'-yl]-2,6-dimethyl-phenyl-methanone

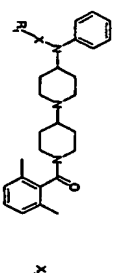


It is prepared from (2,6-dimethyl-phenyl)-(4'-methyl-4-phenylamino-1,4'-bipiperidiny-1'-yl)-methanone and benzyl bromide following a similar procedure as described in example 52. MS/ESI 496 ($\text{M}+\text{H}$) $^+$. The starting material may be prepared from 1'-(2,6-dimethyl-benzoyl)-

- 17 -

4'-methyl-1,4'-bipiperidiny-4-one, by following a similar procedure as described in example 51e) MS/ESI 408 ($\text{M}+\text{H}$) $^+$.

By following the procedure of Example 53 above and using the appropriate starting materials the compounds of formula X_6

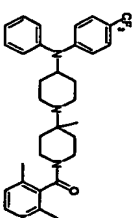


wherein -X-R₁ has the significances as indicated in Table 3 below, may be prepared.

Table 3

Example	-X-R ₁	MS/ESI ($\text{M}+\text{H}$) $^+$
54		517
55		497

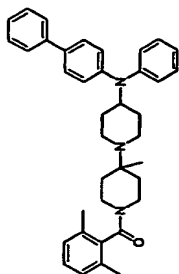
Example 56: (2,4-Dimethyl-pyridin-3-yl)-(4'-methyl-4-[phenyl-(4-trifluoromethyl-phenyl)-amino]-1,4'-bipiperidiny-1'-yl)-methanone



It is prepared from 4-(4-trifluoromethyl-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester by using a procedure as described in example 1. MS/ESI 551 ($\text{M}+\text{H}$) $^+$. The starting material is prepared from 4-trifluoromethyl-phenylamine and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester following a procedure as described in example 51e). MS/ESI 345 ($\text{M}+\text{H}$) $^+$.

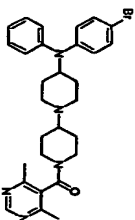
Example 57: [4-(Biphenyl-4-yl-phenyl-amino)-4'-methyl-1,4'-bipiperidiny-1'-yl]-2,6-dimethyl-phenyl-methanone

- 18 -



It is prepared from 4-phenylamino-piperidine-1'-carboxylic acid tert-butyl ester and 4-bromo-biphenyl by using a procedure as described in example 1. MS/ESI 558 (M+H)⁺.

Example 58: {4-[(4-Bromo-phenyl)-phenyl-amino]-1',4'-bipiperidiny-1'-yl}-(4,6-dimethyl-pyrimidin-5-yl)-methanone



It is prepared from [1',4'-bipiperidiny-4-yl-(4-bromo-phenyl)-phenyl-amine and 4,6-dimethyl-pyrimidine-5-carboxylic acid by following a procedure as described in example 1. MS/ESI 548 (M+H)⁺.

[1',4'-bipiperidiny-4-yl-(4-bromo-phenyl)-phenyl-amine used as starting materials may be prepared as follows:

a) 4-(4-Bromo-phenylamino)-piperidine-1'-carboxylic acid tert-butyl ester is prepared from 4-bromo-phenylamine and 4-oxo-piperidine-1'-carboxylic acid tert-butyl ester as described in example 51e). MS/ESI 355 (M+H)⁺.

b) 4-[(4-Bromo-phenyl)-phenyl-amino]-piperidine-1'-carboxylic acid tert-butyl ester is prepared from 4-(4-bromo-phenylamino)-piperidine-1'-carboxylic acid tert-butyl ester and iodo-benzene as described in example 51. MS/ESI 431 (M+H)⁺.

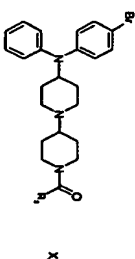
c) (4-Bromo-phenyl)-phenyl-piperidin-4-yl-amine is prepared from 4-(4-bromo-phenyl)-phenyl-amino-piperidine-1'-carboxylic acid tert-butyl ester as described in example 1b). MS/ESI 331 (M+H)⁺.

- 19 -

d) 4-(4-Bromo-phenyl)-phenyl-amino-[1',4'-bipiperidiny-1'-carboxylic acid tert-butyl ester] is prepared from (4-bromo-phenyl)-phenyl-piperidin-4-yl-amine and 4-oxo-piperidine-1'-carboxylic acid tert-butyl ester as described in example 43a). MS/ESI 514 (M+H)⁺.

e) [1',4'-bipiperidiny-4-yl-(4-bromo-phenyl)-phenyl-amine is prepared from 4-(4-bromo-phenyl)-phenyl-amino-[1',4'-bipiperidiny-1'-carboxylic acid tert-butyl ester] as described in example 1b). MS/ESI 414 (M+H)⁺.

By using a procedure as disclosed above and the corresponding starting materials, the compounds of formula X₄

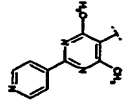
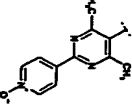


wherein R₂ is as defined in Table 4 below, may be prepared.

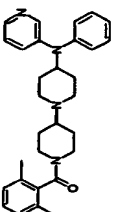
Table 4

Example	R ₂	MS/ESI (M+H) ⁺
59		546
60		587
61		603
62		563
63		564
64		548

- 20 -

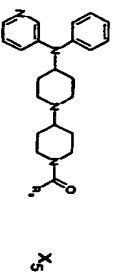
65		625
66		641

Example 67: (2,6-Dimethyl-phenyl)-[4-(phenyl-pyridin-3-yl-amino)-[1,4']bipiperidinyl-1'-yl]-methanone





It is prepared from 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester and 3-bromopyridine by using a procedure as described in example 58 and 58b) to e). MS/ESI 469 (M+H)⁺.

By following a procedure as disclosed above, the compounds of formula X₅






wherein R₂ is as given in Table 5 below, may be prepared.

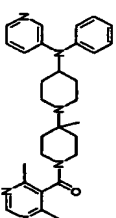
Table 5

Example	R ₂	MS/ESI (M+H) ⁺
68		471
69		510

- 21 -

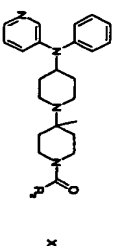
70		526
71		486
72		487

Example 73: (4,6-Dimethyl-pyrimidin-5-yl)-[4'-methyl-4-(phenyl-pyridin-3-yl-amino)-[1,4']bipiperidinyl-1'-yl]-methanone



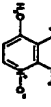
It is prepared from phenyl-piperidin-4-yl-pyridin-3-yl-amino and 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester using a procedure as described in example 1, 1c) and 1d). MS/ESI 485 (M+H)⁺.



By following the procedure as disclosed in example 73, the compounds of formula X₆



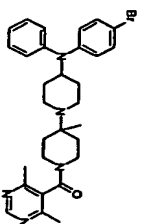
wherein R₂ has the significances as indicated in Table 6, may be prepared.

Table 6

Example	R ₂	MS/ESI (M+H) ⁺
74		500

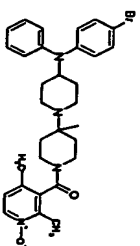
75		540
76		483

Example 77: (4-[(4-Bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidiny-1'-yl)-(4,6-dimethyl-pyrimidin-5-yl)-methanone



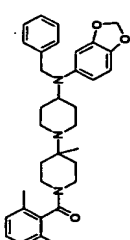
It is prepared from 4-bromo-phenyl)-phenyl-piperidin-4-yl-amine and 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester using a procedure as described in example 1, 1c) and 1d). MS/ESI 562 (M+H)⁺.

Example 78: (4-[(4-Bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidiny-1'-yl)-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone



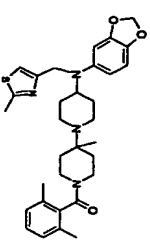
It is prepared from (4-bromo-phenyl)-phenyl-piperidin-4-yl-amine and 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester using a procedure as described in example 1, 1c) and 1d). MS/ESI 577 (M+H)⁺.

Example 79: (4-(Benzol[1,3]dioxol-5-yl-benzyl-amino)-4'-methyl-[1,4']bipiperidiny-1'-yl)-(2,6-dimethyl-phenyl)-methanone



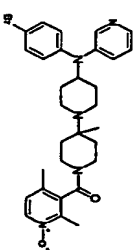
It is prepared from 1'-(2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidiny-4-one and benzol[1,3]dioxol-5-ylamine by following a procedure as described in examples 51 and 52. MS/ESI 540 (M+H)⁺.

Example 80: (4-[1,3-Benzodioxol-5-yl-(2-methyl-thiazol-4-ylmethyl)-amino]-4'-methyl-1,4'-bipiperidiny-1'-yl)-(2,6-dimethyl-phenyl)-methanone



It is prepared from 1'-(2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidiny-4-one and benzol[1,3]dioxol-5-ylamine by following a procedure as described in examples 51 and 52. MS/ESI 561 (M+H)⁺.

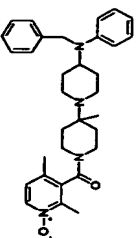
Example 81: (4-[(4-Bromo-phenyl)-pyridin-3-yl-amino]-4'-methyl-[1,4']bipiperidiny-1'-yl)-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone



It is prepared from 4-(pyridin-3-ylamino)-piperidine-1-carboxylic acid tert-butyl ester and 1,4-dibromo-benzene by following a procedure as described in example 1. MS/ESI 578 (M+H)⁺.

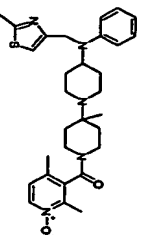
- 24 -

Example 82: [4-(Benzyl-phenyl-amino)-4'-methyl-1,4'-bipiperidin-1'-yl]-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone



It is prepared from phenyl-piperidin-4-yl-amine by following a procedure as described in examples 52 and 1. MS/ESI 513 (M+H)⁺.

Example 83: (2,4-Dimethyl-1-oxy-pyridin-3-yl)-(4'-methyl-4-[(2-methyl-thiazol-4-ylmethyl)-phenyl-amino]-1,4'-bipiperidin-1'-yl)-methanone



It prepared from (4'-methyl-1,4'-bipiperidin-4-yl)-(2-methyl-thiazol-4-ylmethyl)-phenyl-amine using a procedure as described in example 1. MS/ESI 534 (M+H)⁺.

(4'-methyl-1,4'-bipiperidin-4-yl)-(2-methyl-thiazol-4-ylmethyl)-phenyl-amine, used as starting material, is obtained as follows: a mixture of 4-(benzyl-phenylamino)-4'-methyl-1,4'-bipiperidin-1'-carboxylic acid tert.-butyl ester (1.0 g, 2.16 mmol), ammonium formate (0.5 g, 7.92 mmol) and Pd(OH)₂ (20%) on charcoal (0.25 g) in methanol (25 ml) is heated under reflux for 3 h. The catalyst is filtered off and washed with methanol. The solvent is removed and the residue dissolved in ethyl acetate. The organic solution is extracted with 1N NaOH and brine and dried with sodium sulfate. Removal of the solvent gives crude 4'-methyl-4-phenylamino-1,4'-bipiperidin-1'-carboxylic acid tert.-butyl ester which is used in the next step without further purification. MS/ESI 374 (M+H)⁺.

4'-Methyl-4-phenylamino-1,4'-bipiperidin-1'-carboxylic acid tert.-butyl ester is converted into (4'-methyl-1,4'-bipiperidin-4-yl)-(2-methyl-thiazol-4-ylmethyl)-phenyl-amine using a procedure as described in examples 52 and 1(d).

- 25 -

The compounds of formula I in free form or in pharmaceutically acceptable salt form exhibit valuable pharmacological properties, e.g. as CCR5 antagonists, e.g. as indicated in *in vitro* tests and therefore indicated for therapy.

a) CCR5 membrane binding assay

Human CCR5 is used to generate stable transfectants in CHO K1 cells. Membranes prepared from these CCR5 transfectants are used in a radioligand binding assay using 125-I MIP-1α as a ligand and the compounds of formula I are tested for inhibitory activity. The data are reported as IC₅₀, i.e. the concentration of compound required to achieve 50% inhibition of [1-125]MIP-1α binding. In this assay, compounds of formula I have an IC₅₀ ≤ 1 μM. Compounds of Examples 16, 53 and 83 have an IC₅₀ of 2 to 3 nM, respectively.

b) CCR5 functional assay – Ca²⁺ mobilization

Human CCR5 is used to generate stable transfectants in CHO K1 cells. These CCR5 transfectants are used for assessing Ca²⁺ mobilization in response to stimulation by the CCR5 ligands MIP-1α, MIP-1β, HCC-1(9-74) or RANTES. For the assay the cells are loaded with a Ca²⁺-sensitive fluorochrome (Fluo3 or Fluo4). Ligand concentrations between 0.01 - 100 nM are used to induce Ca²⁺ mobilization which is monitored in a fluorometer with appropriate settings.

To assess the activity of the compounds to be tested, a baseline fluorescence reading is taken after which the compounds at the desired concentration are added to the cells and fluorescence is further recorded for a certain time to assess whether compounds show agonistic effects. Next the agonist is added to the mixture and fluorescence monitored. The inhibition of Ca²⁺ flux in the presence of the compounds to be tested is calculated from the inhibition of maximal fluorescence induced by the agonist. IC₅₀ values are calculated from dose-response curves obtained with the compounds. In this assay, compounds of formula I have an IC₅₀ ≤ 1 μM. For example, compounds of Example 1, 18 and 52 have an IC₅₀ of 10, 9 and 4, respectively.

c) CCR5 functional assay – chemotaxis

CCR5 transfectants are generated in Jurkat T cells or the mouse pre B cell line L1.2. Migration of CCR5 transfectants is tested in transwell tissue chamber inserts system with the CCR5 agonist MIP-1α at concentrations of 1-100 nM. Cells migrated in response to the agonist compared to a buffer control are quantified in a flow cytometer. The compounds to be tested are added to the cells and the agonist compartments. IC₅₀ values are calculated

from concentration-response curves obtained with the compounds in the presence of MIP-1 α . In this assay, compounds of formula I have an $IC_{50} \leq 1 \mu M$.

d) Experiments performed in murine animal models show that vessel wall remodeling after experimental injury (e.g. induced by allotransplantation) is significantly inhibited in the absence of functional CCR5.

The compounds of formula I are, therefore, useful in the prevention and/or treatment of diseases or disorders mediated by interactions between chemokine receptors, e.g. CCR5, and their ligands, e.g. In transplantation, such as acute or chronic rejection of organ, tissue or cell allo- or xenografts or delayed graft function, autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, vasculitis, pemphigus anemlia, Sjogren syndrome, uveitis, psoriasis, alopecia areata and others, allergic diseases, e.g. allergic asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, allergic contact dermatitis, inflammatory diseases optionally with underlying aberrant reactions, e.g. inflammatory bowel disease, Crohn's disease or ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye disease, keratoconjunctivitis, myocarditis or hepatitis, ischemia/reperfusion injury, e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, traumatic shock and others, cancer, e.g. solid tumors or lymphatic cancer such as T cell lymphomas or T cell leukemias, metastasizing or angiogenesis, infectious diseases, e.g. toxic shock (e.g. superantigen induced), septic shock, adult respiratory distress syndrome or viral infections, e.g. AIDS. By transplantation is meant allo- or xeno grafts of e.g. cells, tissues or solid organs, for example pancreatic islets, stem cells, bone marrow, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pancreas, trachea or oesophagus. Chronic rejection is also named graft vessel diseases.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.01 to 10 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 1000 mg, conveniently administered,

for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 500 mg active ingredient.

The compounds of formula I may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of formula I in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The compounds of formula I may be administered in free form or in pharmaceutically acceptable salt form e.g. as indicated above. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

- 1.1 A method for preventing or treating disorders or diseases mediated by interactions between chemokine receptors and their ligands, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
- 1.2 A method for preventing or treating acute or chronic transplant rejection or inflammatory or autoimmune diseases, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
2. A compound of formula I or a pharmaceutically acceptable salt thereof for use as a pharmaceutical, e.g. in any of the methods as indicated under 1.1 or 1.2 above.
3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 or 1.2 above comprising a compound of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent or carrier thereof.
4. A compound of formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as in 1.1 or 1.2 above.

- 28 -

The compounds of formula I may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. in immunosuppressive or immunomodulating regimens or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, a chemotherapeutic agent or an anti-infective agent, e.g. an anti-viral agent such as e.g. an anti-retroviral agent or an antibiotic. For example, the compounds of formula I may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a macrocyclic lactone having immunosuppressive properties, e.g. rapamycin, 40-C-(2-hydroxyethyl)-rapamycin, CC1779 or AB1578; an ascomycin having immunosuppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprine; methotrexate; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyaspergualine or an immunosuppressive homologue, analogue or derivative thereof; an accelerating lymphocyte homing agent, e.g. FTY720; monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD11a/CD18, CD25, CD27, CD28, CD40, CD45, CD58, CD80, CD86, CD137, ICOS, CD150 (SLAM), OX40, 4-1BB or to their ligands, e.g. CD154, or antagonists thereof; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4ig (for ex. designated ATCC 68829) or a mutant thereof, e.g. LEA29Y; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or antichemokine antibodies or antichemokine receptor antibodies or low molecular weight chemokine receptor antagonists, e.g. anti MCP-1 antibodies.

Where the compounds of formula I are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory or chemotherapeutic therapy, dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a compound of formula I and at least a second drug substance, e.g. an immunosuppressant,

- 29 -

immunomodulatory, anti-inflammatory, anti-infective or chemotherapeutic drug, e.g. as indicated above.

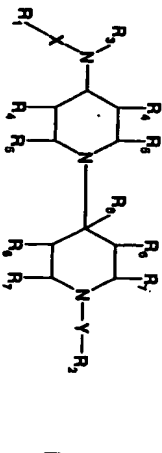
6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a CCR5 antagonist, e.g. a compound of formula I as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory, anti-infective or chemotherapeutic drug. The kit may comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Claims

1. A compound of formula (I)



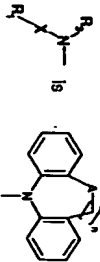
wherein

X is a direct bond; $-\text{CH}_2-$; $-\text{CH}_2\text{CH}_2-$; $-\text{CHPh}-$; $-\text{C}(\text{O})-$; $-\text{O}-$; $-\text{NH}-$ or NR_2 .

R₁ is optionally R₁₀ and/or R₁₁-substituted phenyl; optionally R₁₀ and/or R₁₁-substituted heteroaryl; optionally R₁₀ and/or R₁₁-substituted heteroaryl N-oxide; or optionally R₁₀ and/or R₁₁-substituted naphthyl;

R₂ has one or two significances given for R₁; or is optionally R₁₀ and/or R₁₁-substituted fluorenyl; optionally R₁₀-substituted C₁-C₆ alkyl; optionally R₁₀-substituted C₂-C₆ alkenyl; optionally R₁₀-substituted C₃-C₆ cycloalkyl; optionally R₁₀-substituted adamantyl; or optionally R₁₀-substituted C₄-C₆ cycloalkenyl;

R₃ has one of the significances given for R₁; or is optionally R₁₀ and/or R₁₁; substituted fluorenyl; R₁₀-substituted C₁-C₆ alkyl; optionally R₁₀-substituted C₂-C₆ alkenyl; optionally R₁₀-substituted C₃-C₆ cycloalkyl; optionally R₁₀-substituted adamantyl; or optionally R₁₀-substituted C₄-C₆ cycloalkenyl;



wherein A is -CH₂-, NH-, NHG-, S-, SO-, SO₂- or -O-, n is 0, 1 or 2, and the aromatic rings are each, independently optionally R₁₀-substituted;

each of R₄, independently, has one of the significances of R₅; or is CN; OH; OR₆; F; Cl; Br, or I;

each of R_6 , independently, is H ; C_1 - C_6 alkyl; C_1 - C_6 hydroxyalkyl; C_2 - C_6 alkoxyalkyl; C_1 - C_6 halogenoalkyl; phenyl; benzyl; or heteroaryl;

each of R_6 , independently, has one of the significances given for R_i , each of R_7 , independently, has one of the significances given for R_5 .

R_9 is H; C₁-C₆ alkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; phenyl; benzyl; CN; CH₂NH₂; CH₂NHR₉; CH₂NR₉R₉; CH₂NHC(O)R₉; CH₂NH₂C(O)R₉; CH₂NHC(O)NHR₉; CH₂NR₉C(O)NHR₉; CH₂NR₉SO₂R₉; CH₂NHC(O)OR₉; CH₂NR₉C(O)OR₉; CH₂NHSO₂R₉; CH₂N(SO₂R₉)₂; or CH₂NR₉SO₂R₉;

each R₉, independently, is C₁-C₆ alkyl; C₃-C₆ cycloalkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; phenyl; benzyl; heteroaryl; or CF₃;

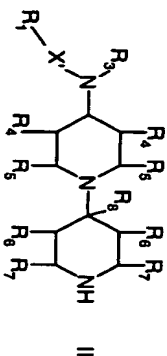
R₁₀ represents to 4 substituents independently selected from C₁-C₆ alky; C₁-C₆ hydroxyalkyl; C₂-C₆ alkoxyalkyl; C₁-C₆ halogenoalkyl; C₃-C₆ cycloalkyl; C₂-C₆ alkenyl; C₃-C₆ cycloalkenyl; C₂-C₆ alkynyl; phenyl; heteroaryl; heterocaryl; heterocaryl N-oxide ; F; Cl; Br; I; OH; OR₆; CONH₂; CONHR₆; CONR₆R₆; OC(O)R₆; OC(O)OR₆; OC(O)NHR₆; OC(O)NHR₆R₆; OSO₂R₆; COOH; COOR₆; CF₃; CHF₂; CH₂F; CN; NO₂; NH₂; NHR₆; NR₆R₆; NHCO(O)R₆; NHCO(O)R₆; NHCO(O)NH₂; NHCO(O)NH₂; NR₆C(O)NHR₆; NR₆C(O)NHR₆; NHCO(O)R₆; NR₆C(O)OR₆; NHCO₂R₆; N(SO₂R₆)₂; NR₆SO₂R₆; SR₆; Si(O)R₆; SO₂R₆; Si(CH₃)₂ and B(OC(CH₃)₂)₂; R₁₁ represents two adjacent substituents which form an annulated 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; and

Y is a direct bond; -C(O)-; -C(O)CH₂-; -S(O)-; -S(O₂)-; -C(S)-; -CH₂-; -C(-CH₂CH₂-); -CH(R₅-) or -C(R₄)₂;

in free form or in salt form.

2. A compound according to claim 1, wherein R_1 is phenyl or heteroaryl, each being optionally substituted by R_{10} ; or phenyl optionally substituted by R_{11} ; wherein R_{10} represents 1 to 3 substituents independently selected from C_1 - C_6 alkyl; C_1 - C_6 hydroxyalkyl; C_2 - C_6 alkoxyalkyl; C_1 - C_6 halogenoalkyl; C_2 - C_6 cycloalkyl; C_2 - C_6 alkenyl; C_3 - C_6 cycloalkenyl; C_2 - C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR₆; CONH₂; CONHR₆; CONR₆R₆; OC(O)R₆; OC(O)OR₆; OC(O)NHR₆; OC(O)NR₆R₆; OSO₂R₆; COOH; COOR₆; CF₃; CHF₂; CH₂F; CN; NO₂; NH₂; NHR₆; NR₆R₆; NHC(O)R₆; NR₆C(O)R₆; NHC(O)NHR₆; NHC(O)NH₂; NR₆C(O)NHR₆; NR₆C(O)NR₆R₆; NHC(O)OR₆; NR₆C(O)OR₆; NHCO₂R₆; N(SO₂R₆)₂; NR₆SO₂R₆; SR₆; Si(O)R₆; SO₂R₆ and Si(CH₃)₃ and R₁₁ is an annulated 5 or 6 membered non aromatic ring optionally containing 1 or 2 oxygen atoms, and attached to 2 adjacent carbon atoms.

3. A compound according to claim 1, wherein each of R_4 , R_5 , R_6 or R_7 independently, is H; C_{1-6} alkyl; or benzyl.
4. A compound according to claim 1, wherein R_9 is H; C_{1-6} alkyl; or C_{2-6} alkenyl.
5. A compound according to claim 1 wherein X is a direct bond or $-CH_2-$ and / or Y is $-C(O)-$.
6. A process for the preparation of a compound of formula I according to claim 1, which process comprises
 - a) for the preparation of a compound of formula I wherein X is a direct bond, $-CH_2-$, $-CH_2-CH_2-$ or $-CHR_R-$ and Y is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O)_2-$, amidating a compound of formula II

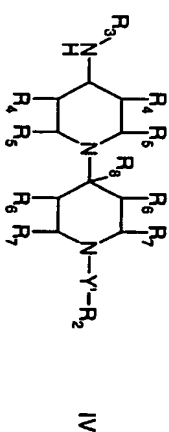


wherein R_1 and R_2 are as indicated above and X' is a direct bond, $-CH_2-$, $-CH_2-CH_2-$ or $-CHR_R-$ with a compound of formula III



wherein R_2 is as defined above, Y' is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O)_2-$ and A' is a leaving group, e.g. Cl, Br or OH,

- b) for the preparation of a compound of formula I wherein X is a direct bond and Y is $-CH_2-$, substituting a compound of formula II as defined above wherein X' is a direct bond, to a reductive amination; or
- c) for the preparation of a compound of formula I wherein X is CH_2- , $-CH_2-CH_2-$ or $-CHR_R-$ and Y is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O)_2-$, reacting a compound of formula IV



wherein R_2 to R_9 and Y' are as defined above, with a compound of formula V



wherein R_1 is as defined above and X'' is CH_2- or $-CHR_R-$,

and, where required, converting the resulting compound of formula I obtained in free form into the desired salt form, or vice versa.

7. A compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.
8. A pharmaceutical composition comprising a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent a carrier thereof.
9. A pharmaceutical combination comprising
 - a) a first agent which is a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, and
 - b) at least one co-agent.
10. A method for preventing or treating disorders or diseases mediated by interactions between chemokine receptors and their ligands, in a subject in need of such a treatment, which method comprises administering to said subject an effective amount of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/EP 02/03871A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58 C07D401/14 C07D211/96 C07D417/14 A61K31/4468B. FIELD OF SEARCH
Within document searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation in the extent that such documents are included in the index searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 66559 A (MCCOMBIE STUART M; CLADER JOHN M (US); SCHERING CORP (US); JOSTEN 9 November 2000 (2000-11-09) page 1, line 10 -page 2, line 22 claim 1	1-10
X	DE 196 43 331 A (THOMAE GNBH DR K) 23 Apr'1 1998 (1998-04-23) claim 1	1-4
A, P	WO 01 98268 A (DU PONT PHARM CO) 27 December 2001 (2001-12-27) claims 1, 17	1, 10
A	WO 00 76972 A (GUTHIKONDA RAVI N; KIM DOOSEOP (US); OATES BRYAN (US); CHAPMAN KEV) 21 December 2000 (2000-12-21) claims 1, 34	1, 10
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- * document defining the general state of the art which is not considered to be of particular relevance
 * document published after the international filing date but prior to the date of publication of the international patent application
 * document which may have doubt on priority (claiming) or which may have doubt on the date of publication of another document referring to an oral disclosure, use, exhibition or other means
 * document published prior to the international filing date but later than the priority date claimed
 * document number of the same patent family

6 August 2002

23/08/2002

Name and mailing address of the ISA

European Patent Office, P. B. 5818
NL - 2280 HV Rijswijk
Tel: (+31-70) 346-2000, Tx: 31 651 epo nl,
Fax: (+31-70) 346-5010

Authorized officer

Famnl, S

Form PCT/IB4210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/EP 02/03871

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 02 22592 A (SCHERING CORP) 21 March 2002 (2002-03-21) page 79; examples 286, 287 claim 1	1
A	WO 98 11128 A (EBERLEIN WOLFGANG; ENTZEROTH MICHAEL (DE); HALLERMAIER GERHARD (DE) 19 March 1998 (1998-03-19) page 125; examples 565, 566 claim 1 page 127; claims 584, 587, 588	1
A	WO 98 11082 A (DINOUJIS NIKOLAOS; FRIEBE WALTER GUNAR (DE); MICHAELIS UWE (DE); K) 19 March 1998 (1998-03-19) examples 20, 27, 32 claim 1	1

Form PCT/IB4210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 02/03871

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Continuation of Box I.1

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos. because they relate to subject matter not required to be searched by the Authority, namely: see FURTHER INFORMATION sheet PCT/ISA/210

2. ☐ Claims Nos. because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos. because they are dependent claims and are not defined in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International Application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, the Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/EP 02/03871

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0066559	A	09-11-2000	
		AU 4501000 A	17-11-2000
		BR 0010607 A	13-02-2002
		CN 1349504 T	15-05-2002
		CZ 20013941 A3	17-04-2002
		EP 1175402 A1	30-01-2002
		NO 20015365 A	03-01-2002
		TR 200103213 T2	21-03-2002
		WO 0066559 A1	09-11-2000
DE 19643331	A	23-04-1998	
		DE 19643331 A1	23-04-1998
		AU 4867497 A	15-05-1998
		WO 9817646 A1	30-04-1998
WO 0198268	A	27-12-2001	
		AU 6860701 A	02-01-2002
		WO 0198268 A2	27-12-2001
WO 0076972	A	21-12-2000	
		AU 5472600 A	02-01-2001
		EP 1192133 A1	03-04-2002
		WO 0076972 A1	21-12-2000
		US 6358979 B1	19-03-2002
WO 0222592	A	21-03-2002	
		AU 9454701 A	26-03-2002
		WO 0222592 A2	21-03-2002
WO 9811128	A	19-03-1998	
		DE 19636623 A1	12-03-1998
		DE 19720011 A1	19-11-1998
		AU 721035 B2	22-06-2000
		AU 4119697 A	02-04-1998
		B6 103250 A	31-05-2000
		BR 9712023 A	31-08-1999
		CN 1230196 A	29-09-1999
		CZ 9900823 A3	16-06-1999
		EE 9900115 A	15-10-1999
		WO 9811128 A1	19-03-1998
		EP 0927192 A1	07-07-1999
		HR 970481 A1	31-08-1998
		JP 2000505100 T	25-04-2000
		NO 991130 A	05-05-1999
		NZ 334543 A	23-06-2000
		PL 331989 A1	16-08-1999
		SK 29799 A3	13-03-2000
		TR 9900537 T2	21-07-1999
		US 6344449 B1	05-02-2002
		ZA 9708083 A	17-12-1999
		HU 9904501 A2	28-04-2000
WO 9811082	A	19-03-1998	
		DE 19637043 A1	19-03-1998
		AU 741636 B2	06-12-2001
		AU 4384197 A	02-04-1998
		BR 9712818 A	21-12-1999
		CN 1237161 A . B	01-12-1999
		WO 9811082 A1	19-03-1998
		EP 0927174 A1	07-07-1999
		JP 2001504806 T	10-04-2001
		TR 9901200 T2	21-10-1999
		ZA 9708170 A	11-03-1999

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☒ OTHER: side to B

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.